

Correlation between Hemoglobin A1c (HbA1c) and Average Blood Glucose: Can HbA1c Be Reported as Estimated Blood Glucose Concentration?

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Glycation is the nonenzymatic addition of sugar to amino groups of proteins. While virtually any protein in the body can be glycosylated, for convenience and ease of obtaining a sample, glycosylated hemoglobin is measured in the blood obtained from a patient. Blood glucose concentrations exhibit wide diurnal fluctuations due to food ingestion, exercise, and other factors. In contrast, the concentration of glycosylated hemoglobin remains relatively stable with time. This is due to the life span of red blood cells, which is usually ~120 days. In individuals with a normal erythrocyte life span, glycosylated hemoglobin is directly proportional to the blood glucose concentration over the preceding 8 to 12 weeks.¹

In patients with diabetes mellitus, the glycosylated hemoglobin value is used to determine the degree of glycemic control and to make decisions regarding therapy.^{2,3} In addition, the concentration of glycosylated hemoglobin predicts the progression of diabetic microvascular complications. This has been clearly documented by randomized, multicenter studies in patients with type 1⁴ and type 2⁵ diabetes. More recent evidence indicates that glycosylated hemoglobin also predicts cardiovascular disease in patients with type 1 diabetes.⁶ Measurement of glycosylated hemoglobin is thus an essential component in the management of patients with diabetes.

There are several forms of glycosylated hemoglobin. These include hemoglobin A1c (HbA1c), HbA1 (which comprises HbA1a, HbA1b, and HbA1c), and total glycosylated hemoglobin (which comprises HbA1 plus other glycosylated hemoglobin species). Both the Diabetes Complications and Control Trial (DCCT) and the United Kingdom Prospective Diabetes Study measured HbA1c.^{4,5} Thus, most clinical outcome data that relate glycemic control to the complications of diabetes are based on HbA1c measurement. The American Diabetes Association (ADA) recommends that HbA1c should be measured at least twice a year in persons with diabetes.^{1,2}

Retrospective analysis of data derived from self-monitoring of blood glucose by patients in the DCCT identified a linear correlation between HbA1c and average blood glucose concentrations.⁷ Although the number of subjects enrolled was large, the DCCT was not designed to determine average blood glucose and the patient population was limited to individuals with type 1 diabetes. A number of other studies have also examined this relationship,⁸⁻¹⁰ but are limited by the inclusion of relatively few subjects and few glucose assays. Therefore, a large multinational study is being conducted to establish whether average blood glucose concentration correlates with HbA1c and, if so, to determine a conversion factor.

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Abbreviations: (ADA) American Diabetes Association, (ADAG) A1c-derived average glucose, (CGM) continuous glucose monitoring, (DCCT) Diabetes Complications and Control Trial, (eAG) estimated average glucose, (EASD) European Association for the Study of Diabetes, (HbA1c) hemoglobin A1c

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The study is named ADAG, for estimated A1c-derived average glucose. The planned study group comprises 700 individuals (300 with type 1 diabetes, 300 with type 2 diabetes, and 100 healthy subjects). Subjects have been recruited in several different countries to obtain diverse racial and ethnic representations. Individuals with different HbA1c concentrations, namely 4–6.5%, 6.6–8.5%, and >8.5% (reference range for HbA1c is 4–6%), have been targeted. HbA1c was measured monthly with all analyses performed in a single laboratory to minimize assay variation. It is more difficult to accurately measure average blood glucose than HbA1c. In order to evaluate average glucose, all study participants underwent continuous glucose monitoring (CGM) (using a MiniMed device) for 48 hours every month for 4 months. During CGM, subjects perform an eight-point assessment of blood glucose using a HemoCue meter. In addition, all participants measured their blood glucose concentration seven times per day, at least 3 days per week, for the entire duration of the 12-week study. Thus, over 2500 glucose measurements were performed in each subject over the course of the study.

Preliminary findings of the ADAG study were disclosed at the annual meeting of the European Association for the Study of Diabetes (EASD) in Amsterdam in September 2007. Oral presentations were made at an EASD/ADA symposium and nothing has been published at the time of writing this editorial. Sixty-eight percent of the total participants had completed the study when the presentations were given. Linear regression analysis of this population reveals a good correlation between HbA1c and average blood glucose. Importantly, subgroup analysis of the population who had completed the study indicates essentially uniform findings. There is no significant difference in the regression equation between males and females, healthy controls or subjects with diabetes, individuals with type 1 or type 2 diabetes, and individuals of different ages. These results are not unexpected in light of the knowledge that glycation is a nonenzymatic process, which does not appear to be altered substantially by these factors. Nevertheless, the data are reassuring and will enable a single equation to be used for the vast majority of individuals. Importantly, the correlation fulfilled a priori criteria for acceptance. Therefore, once the study has been completed (anticipated by the end of 2007), a regression equation will be derived that will permit conversion of HbA1c results into estimated average glucose (eAG) values.

What are the implications of the study? The outcome is likely to impact both patients and all health care workers, including clinicians, nurses, educators, and laboratory

personnel, involved in the management of patients with diabetes. It is likely that many laboratories will use the final regression equation to calculate an eAG value based on the HbA1c result. This eAG value could be provided in addition to the measured HbA1c concentration. This would be analogous to the current reporting of the estimated glomerular filtration rate, which is derived from the measurement of serum creatinine, along with the measured creatinine value. Laboratories would report eAG in International System of Units (i.e., mmol/liter) or in milligrams per deciliter, consistent with the method of reporting glucose concentrations in that laboratory. Many clinicians believe that it will be easier to communicate eAG than HbA1c to patients. This will avoid the confusion of discussing “hemoglobin” with patients in relation to their control of blood glucose. Published studies indicate that many patients do not know whether they had a recent HbA1c measurement or its value^{11,12} and it is hoped that an explanation of eAG will reduce this lack of knowledge.

As with most studies, ADAG suffers from some limitations. The number of Asian subjects is low (the involvement of a subgroup planned for India was not realized). Thus, the two countries with the largest numbers of patients with diabetes, namely India and China, are not represented. In addition, no children were included in the study. Although the results met a priori criteria for acceptance, the initial analysis suggests that different individuals with a particular HbA1c concentration could have somewhat different eAG. Further analysis of data might reveal the mechanism underlying this observation. For example, the magnitude of the variation in glucose concentration could contribute to this finding. Finally, an extensive (and expensive) education campaign is necessary to convey the new information to both patients with diabetes and those involved in their management.

Notwithstanding these caveats, the results generated by this study will considerably enhance our comprehension of the relationship between HbA1c and average blood glucose. Data will provide, for the first time, an equation that permits accurate conversion of HbA1c values to eAG. We eagerly look forward to the final results of the study and it is hoped that the findings will lead to improved care of patients with diabetes.

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